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THE AMINO ACIDS IN NUTRITION

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THE AMINO ACIDS IN NUTRITION

One hundred and twenty-five years ago the first amino acid was discovered by the French scientist, Braconnot. Ten years ago Rose, at the University of Illinois, discovered the twenty-second of these unique "building stones" of the proteins. The century between these two discoveries witnessed some of the most exciting achievements in the history of chemistry. Of major interest to nutritionists and biochemists, however, is perhaps that phase of the story which took place in the remarkably brief span of eight years, beginning in 1930 with the classic experiments of Rose and coworkers.

These experiments, preceded by the pioneer studies of Osborne and Mendel in the United States and Abderhalden and others abroad, crystallized the brilliant findings of historic research by elucidating, in terms of nutritional significance, the essential nature of some of these compounds and the indispensability of the remainder in the biochemistry of living organisms.

The amino acids and the proteins which they constitute occupy a unique role in nutrition. Unlike the carbohydrates and fats, which are utilized chiefly as fuel material, the amino acids are used mainly in the synthesis of living tissue. As Rose has remarked, "One of the most astounding attributes of living things is the unerring accuracy with which specific tissue components are manufactured out of the variable mixtures of amino acids circulating in the blood" (1). It is not surprising, therefore, that the nutritional role of the amino acids should have stimulated considerable interest among investigators in biochemistry.

Early Investigations:

Although more than half of the accepted twenty-two amino acids had been discovered before 1900, very little was known concerning their individual functions and actual distribution in various food proteins. Therefore, it was not at first recognized that the nutritive value of a protein depends upon the nature of its amino acid constituents. Attention was focused on total protein intake rather than on the quality or type of protein ingested. As new chemical methods for the separation of the various classes of amino acids became available, knowledge concerning protein chemistry advanced rapidly. The relationship between amino acid composition and the nutritive adequacy of certain proteins finally became apparent and it was soon appreciated that fundamental knowledge of protein metabolism could be obtained only through a knowledge of the behavior and biological significance of the individual amino acids.

(Proteins): With the realization of the basic importance of amino acids in elucidating protein biochemistry, attention was directed to finding out which of the known amino acids are indispen ble and which can safely be excluded from the diet without interfering with normal physiological processes.

From 1912 until about 1930, a great many investigators devoted their efforts towards solving this problem. Although a vast amount of information was derived from these early studies, the limitations of the crude methods then available precluded he establishment of absolutely conclusive results. At that time most of the amino acids were not yet available in pure form, so that it was not possible simply to remove and then restore one or more of these from the experimental diet and observe the resultant effect. Inste l diets were devised in which the sole source of nitrogen was suppl d in the form of a single purified protein known to be low in or completely devoid of one or more of the amino acids. If such a prote.n failed to maintain growth or life and if the failure could be remedied by supplementing the diet with another protein containing the r. issing amino acid or acids it was assumed that the supplementary amino acids were indispensable in the diet. A modification of this early procedure involved the feeding of diets containing hydrolyzed proteins (broken down into their component amino acids) from which certain amino acids had been removed as completely as available methods permitted.

The pioneer studies of Osborne and Mend ' constituted a basic piece of research on the question of the indis nsability of certain amino acids. In one of their first experiments (;) they demonstrated that rats could be maintained for several months on a diet in which wheat gliadin is the only protein. They observ ed, however, that the animals failed to grow on such a diet until the amino acid lysine was added (3) . This constituted the first conclusive evidence that lysine is indispensable for purposes of growth. In li e manner, using the corn protein, zein, Osborne and Mendel (3) howed that not only lysine, but the amino acid tryptophane or a source thereof is also essential for animal growth. In the absence of either lysine or tryptophane, growth ceased and death eventually resulted.

Similar studies along these lines were conducted by numerous other investigators on all of the twenty-one amino acids then known. A complete review of these remarkable early studies has been given by Rose (1) . Although a great deal of presumptive evidence w as presented during this early period for the indispensability of certain amino acids and the apparent dietary unimportance of others, evidence of a conclusive nature was reported for only three amino acids—

lysine, tryptophane and histidine, each of which was demonstrated to be absolutely essential in the diet of experimental animals.

(Pure Amino Acids): The use of known mixtures of pure amino acids in place of proteins in test diets permitted a more precise approach to the understanding of the nutritional significance of these compounds. This method of study was tried with dogs as early as 1912 by Abderhalden (5). Sixteen amino acids were used in the mixture. The experiment was not very successful, however, and the animals failed to thrive on the diet, although it was reported that they were successfully maintained in nitrogen balance for about a week. About four years later, Hopkins (6) reported that rats fed the amino acids cystine, tyrosine, lysine, tryptophane and histidine (now known to be among the essential amino acids) as the only source of nitrogen could be maintained in apparent health for a long time and exhibited only a very slow loss of weight. Replacement of these five amino acids by leucine, valine, alanine, glycine and glutamic acid (only two of which are now known to be essential) resulted in rapid loss of weight and death of the animals. Similar studies were reported by Osborne and Mendel (7), Mitchell (8), Suzuki *et al* (9) and others. None of these experiments were entirely successful, although some glimmerings of light were obtained through them.

In 1930, the now classic experiments in Rose's laboratory were begun. At that time twenty-one amino acids were known. Of these, nineteen were used. The remaining two were unavailable. Also, they had been conclusively demonstrated to be unessential in the diet. Since the milk protein casein had long been used as the most successful source of dietary protein in experimental diets, the mixture of nineteen amino acids was formulated in amounts closely approximating their occurrence in casein. Despite the apparent perfection of this amino acid mixture, the animals failed to grow and exhibited marked loss of appetite (10).

(Discovery of Threonine): These findings led Rose to believe that the growth-promoting proteins contain at least one dietary essential other than the twenty-one amino acids then recognized, and that the nutritive failure of their animals on the synthetic diets was due to the absence of this unknown constituent. This hypothesis was confirmed by the observation that an immediate growth improvement resulted with the substitution of a small amount of casein, gliadin or gelatin for an equivalent amount of the amino acid mixture (11). Since casein seemed to be the most effective protein supplying the missing nutrient, it was selected for further study. The milk protein was hydrolyzed and the resulting amino acids separated into five dif-

ferent fractions according to their physico-chemical properties. Four of these fractions showed little or no growth-stimulating effect. The fifth, or monoamino acid group, was found to be more potent than even casein. Unfortunately, the unknown substance was intimately associated with the essential amino acid, isoleucine, a fact of which the investigators were unaware. This greatly hampered the discovery of the unknown compound, for the crude active protein fraction when fed not only furnished the unknown, but compensated for any isoleucine deficiency as well. It took nearly four years for the "dual nature" of the unknown to be recognized and for it to be separated from the contaminating isoleucine (12). With this accomplished it was relatively easy to isolate and identify the unknown which was found to be a new amino acid (13). Because of its close relationship to the sugar threose, the new amino acid was named threonine (14).

Essential and Non-Essential Amino Acids:

While attempts to isolate the unknown growth essential, threonine, were going on, Rose and coworkers conducted a series of experiments designed to determine the nutritive importance of certain of the *known* amino acids. In these experiments, mixtures of all the known amino acids in pure form were used plus a protein concentrate supplying the as yet undiscovered amino acid, threonine. By omitting one or more of the known amino acids, a nutritional deficiency could be expected if the amino acids in question were indispensable and if the concentrate was not contaminated with them.

The first of these experiments dealt with the nutritive importance of phenylalanine and tyrosine (15). These two amino acids are closely related in chemical structure and for many years had been thought to be mutually interchangeable in metabolism. They are of particular interest also because of their structural similarity to the important hormones, thyroxine and adrenalin. The experimental diets contained purified nutrients, vitamin supplements, the amino acid mixture and the crude protein concentrate. The amino acid mixture, composed of painstakingly purified amino acids collected over a period of seven years prior to these experiments, was made to approximate the composition of casein with the exception that phenylalanine and tyrosine were omitted. On this diet the animals failed to grow. The addition of phenylalanine and tyrosine to the diet resulted in immediate marked gains in weight. The addition of phenylalanine alone resulted in growth equivalent to that obtained with both amino acids. The addition of tyrosine alone failed to prevent the rapid loss of weight observed on the original diet (Chart I).

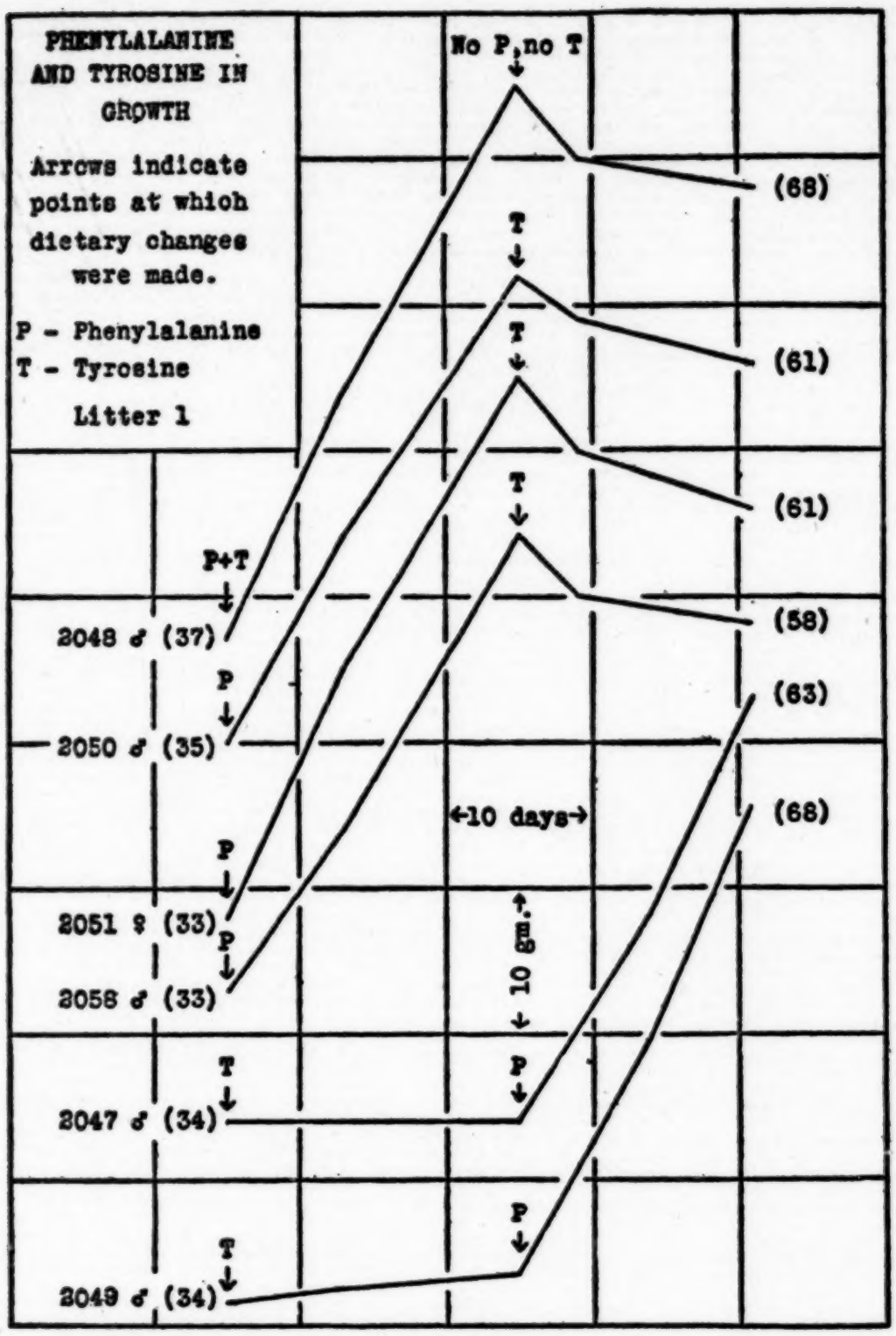

CHART I. The numbers in parentheses denote the initial and final weights of the rats.

These results demonstrated conclusively that phenylalanine is an indispensable dietary component. They also showed that tyrosine, despite its close chemical similarity to phenylalanine, is entirely unable to replace it. Thus phenylalanine was added to the early list of indispensable amino acids, bringing the total at that date to four amino acids — tryptophane, lysine, histidine, phenylalanine.

In a similar fashion, experiments were conducted with the amino acids leucine, isoleucine and norleucine (16). When all three were omitted, nutritive failure and weight loss resulted. Addition of one of the leucines without the others failed to improve conditions. Of the three possible combinations of two leucines each, only that containing leucine and isoleucine was capable of supporting growth.

With the availability of threonine in pure form, the classification of the remaining amino acids was greatly facilitated. Even with this

valuable advance, a great deal of tedious work remained to be done. Almost all of the amino acids had to be recrystallized from three to ten times to render them completely free of interfering substances. correct isomeric forms of leucine, for example, had to be used since the natural form was frequently contaminated with methionine. Despite these difficulties involving extra work, time and patience the experiments proceeded at a remarkable pace and led to many surprising discoveries. Among these was the fact that cystine, long regarded by previous investigators as indispensable, could be replaced by methionine; also that lack of valine not only caused rapid weight loss, but unlike any amino acid heretofore studied, resulted in specific deficiency symptoms apparently related to the nervous system (1).

By 1938, barely eight years after their initial experiments, Rose and coworkers had arrived at a final classification of the amino acids with respect to their indispensability as dietary factors *using growth response as the ultimate criterion* (Table I). Of twenty-two amino acids, only ten were shown to be dietary essentials, while the remaining twelve could be dispensed with without exerting any adverse effects upon the growth process.

Table I. Final classification of the amino acids with respect to their growth effects in experimental animals.†

Indispensable	Dispensable
Lysine	Glycine
Tryptophane	Alanine
Histidine	Serine
Phenylalanine	Norleucine
Leucine	Aspartic acid
Isoleucine	Glutamic acid
Threonine	Hydroxyglutamic acid
Methionine	Proline
Valine	Hydroxyproline
*Arginine	Citrulline
	Tyrosine
	Cystine

*Arginine can be synthesized by the animal organism, but not at a sufficiently rapid rate to meet the demands of *normal* growth.

†Rose (1) has investigated the relative nutritive values of the optical isomers of the essential amino acids (except arginine). He reports that only the naturally occurring forms of valine, leucine, isoleucine, lysine and threonine are effective for the rat, whereas both isomers of tryptophane, phenylalanine, methionine and histidine are utilized.

Amino Acids in Human Nutrition:

A few years after the culmination of Rose's brilliant work in classifying the amino acids, interest arose in the direct investigation of human amino acid requirements and in the experimental study of possible amino acid deficiency symptoms in man. Maintenance of normal nitrogen balance served as the criterion for judging the essential nature of the amino acids under investigation.

Among the earliest of such studies were those reported by Holt and coworkers (17) at Johns Hopkins University. In the first of their experiments four normal adult men were kept on a diet deficient in tryptophane for periods of two to five weeks. The experimental diet consisted of fats, starch, sugar, certain fruits and vegetables low in protein (tomatoes, mushrooms, carrots, asparagus, apples, oranges, etc.), and a synthetic vitamin supplement. Of the total nitrogen ingested only 10 per cent was in the form of food proteins, the remaining 90 per cent being supplied as a mixture of pure amino acids devoid of tryptophane. A few days after the ingestion of the tryptophane-deficient diet each of the subjects went into negative nitrogen balance. Within a week after the restoration of tryptophane to the diet, nitrogen equilibrium was restored in all cases. (Chart II).

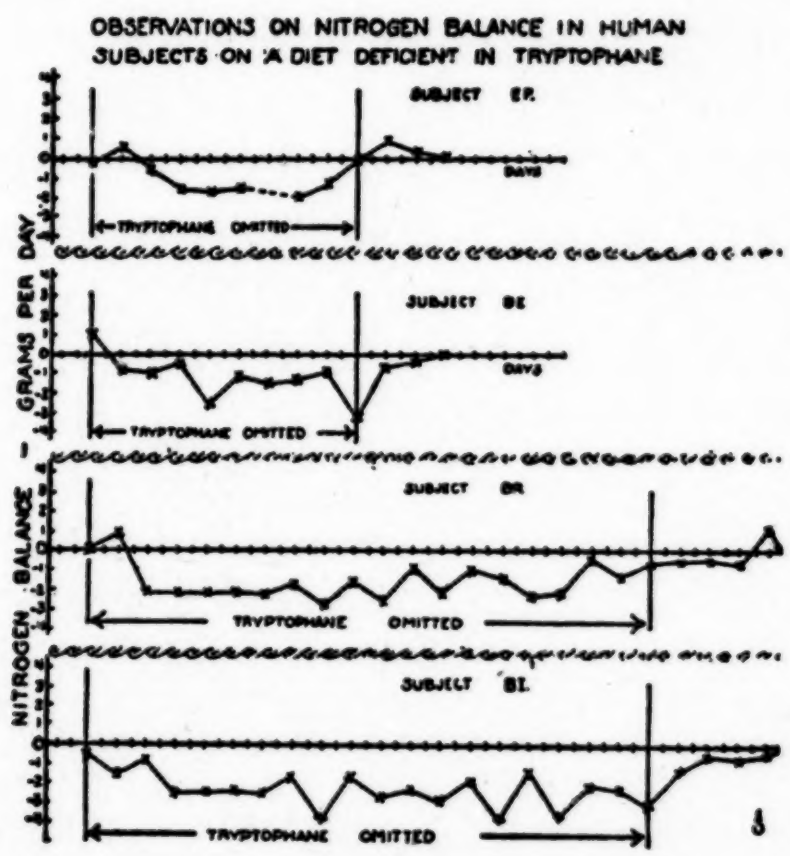

Chart II.

From this the authors conclude that nitrogen equilibrium cannot be maintained in the dietary absence of tryptophane and that this amino acid must therefore be regarded as a dietary essential for man.

In a similar experiment, the human need for lysine was also established (18). Further observations on reactions during lysine deficiency

brought out the unexpected fact that specific deficiency symptoms and a biochemical defect occur during lysine deprivation (19). In addition to the occurrence of a negative nitrogen balance, the lysine deficient subjects all exhibited symptoms of nausea, dizziness and hypersensitivity to metallic sounds five days after being on the experimental diet. The only detectable abnormal biochemical sign, aside from the negative nitrogen balance, was a marked increase in the urinary excretion of non-ketone organic acids. This biochemical defect appears to be characteristic of lysine deficiency, not having been encountered in deficiencies of any other amino acids studied by these workers. The investigators point out, however, that abnormal excretion of organic acids of this type have been reported by other workers in cases of pneumonia, nephrosis, malnutrition, rickets, premature infants, etc., and therefore speculate upon the possibility that an abnormality of lysine metabolism may occur in these conditions.

In another experiment with arginine, Holt *et al* (20) demonstrated that this amino acid appears to be a dietary essential for the male, normal spermatogenesis being maintained only when arginine was present in the diet.

In 1943, Albanese, Holt and coworkers (21) reported additional amino acid studies with humans using methionine and cystine. Using their routine procedure they demonstrated, on the basis of maintenance of nitrogen equilibrium, that methionine is a dietary essential for man. The dietary importance of methionine aside from its role as an essential amino acid has also been pointed out by du Vigneaud *et al* (22) * who demonstrated its ability to serve as a source of essential labile methyl groups. The results obtained with cystine were not sufficiently conclusive to permit any decision as to its possible need in the human diet. Clinical studies were made on the subjects to determine any possible objective deficiency symptoms, but results of these have not yet been published.

While the studies at Johns Hopkins were in progress, work was continuing at Rose's laboratory at the University of Illinois. Following up their animal studies in which it had been shown that only ten of the twenty-two generally recognized amino acids are essential for growth and maintenance, they decided to maintain human subjects on a diet in which more than 95 per cent of the nitrogen was furnished by these ten amino acids. They found that with a daily nitrogen intake of about seven grams, normal nitrogen equilibrium could be maintained. The fact that this low level of nitrogen intake (roughly

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*See also *Borden's Review of Nutrition Research*, October, 1942.

5 grams of protein) *, supplied chiefly as the ten amino acids, readily upported nitrogen equilibrium, led them to conclude that the re-aining twelve amino acids dispensable for animals are also dispen-able for man. Their investigations, therefore, centered on the role f the ten amino acids known to be essential to animals.

This work has not yet been reported in detail, but some prelimi-ary reports have already appeared on the subject. In the first of these (23) valine was removed from the experimental diet described and he other amino acids increased correspondingly to provide a constant itrogen intake. Immediately each subject manifested a negative itrogen balance. Restoration of valine to the diet resulted in a rapid eestablishment of nitrogen equilibrium. Similar, though not as marked, behavior resulted when methionine was removed from the diet. It was concluded, therefore, that both valine and methionine are dietary essentials for man as well as for animals.

In a subsequent report, Rose *et al* (24) showed in the same man-ner that threonine, leucine, isoleucine and phenylalanine are essential in the human diet. A most unexpected result was encountered with histidine. Removal of this amino acid from the diet had no effect on nitrogen equilibrium. Careful rechecking of the diets confirmed this fact. The conclusion reached, therefore, was that histidine although essential for animals is not necessary for the maintenance of nitrogen equilibrium in man. Latest reports from Rose's laboratory (25) bring the total of essential amino acids for man to eight, adding tryptophane and lysine to the previous list. Some doubt exists as to the probable significance of arginine, although as Holt and coworkers have suggested, this may have a function in normal spermatogenesis.

Further experiments are now under way in Rose's laboratory to determine minimum daily requirements of the eight amino acids for the average male adult. Final determination of the exact quantitative and qualitative amino acid requirements of human beings will be of practical value in calculating protein requirements more accurately, and in evaluating more precisely the biological significance of specific protein foods. Knowledge of exact amino acid requirements will also be of considerable importance in problems associated with the use of amino acid mixtures in parenteral alimentation and in shock therapy.

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*The National Research Council recommends a daily protein intake of 70 grams for the average 70 kilogram man.

Dietary Value of Proteins:

The establishment of eight amino acids as dietary essentials fo man and of ten amino acids as essentials for certain test animals is o special practical significance in the nutritional evaluation of a pro tein. Because of the wide variation in amino acid make-up of indi vidual proteins, it is necessary to consider not only the quantitative but the qualitative nature of the proteins in the diet. Recent im proved methods for the determination of amino acids in foods hav contributed greatly to the classification of proteins on this importan basis. The so-called complete protein is one which provides all of th essential amino acids in adequate amounts. Common food source providing high quality complete proteins are meat, fish, eggs, milk cheese, ice cream, soybeans, etc.

It is interesting to note that if equal amounts (100 gm.) of pro tein, supplied by meat and milk are compared, it is found that mil meets the optimal daily requirement for all the essential amino acid by more than 100 per cent while meat meets the tyrosine and valin requirements by less than 100 per cent (26). This is an important factor in considering the economic aspects of diets. Combinations o two or more of the incomplete, cheaper protein foods – those no containing all or sufficient amounts of the essential amino acids – i another way to provide adequate protein nutrition economically i the proteins are selected so that the amino acid deficiencies of one are supplemented by the amino acids provided by the other.

Future research in amino acid and protein nutrition undoubtedly will deal largely with the problems of which amino acids are required in the diet, the minimal requirements of each of these and the specific functions, in addition to the maintenance of nitrogen balance, which they may have. As these problems become more clearly defined, procedures for the quantitative determination of the amino acids in typical proteins will assume increasing importance as a means of evaluating the nutritive values of individual proteins and protein combinations in the diet.

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NEWS DIGEST

VITAMINS IN BEVERAGES—Beverages made from commercial meat extracts are rich in riboflavin and niacin; beer, studies made in England show, also supplies both of these vitamins; tea adds traces of riboflavin to the diet, and coffee provides a little niacin. Half a pint of one of the beers tested would furnish almost half the daily requirement of niacin and 15 to 30% of the riboflavin. A cup of tea contains about one two-hundredths of the daily requirement of riboflavin, and a cup of coffee about one hundredth of the daily requirement of niacin.—*Abst. Mod. Med. 12,* 203 (1944).

GLUCOASCORBIC ACID—Glucoascorbic acid, a compound related to the vitamin ascorbic acid, has been found to produce a scurvy-like condition in guinea pigs. By means of a newly developed highly purified ration for these animals it is possible to provide a diet free of an unidentified protective substance, formerly contained in standard diets for this animal. Guinea pigs on the new diet, which provides only 0.1 mg. of ascorbic acid daily, were fed glucoascorbic acid and within 10 days developed a disease characterized by failure of growth, diarrhea, alopecia, mild hemorrhage and death. Control animals on the same diet, but which did not receive the glucoascorbic acid, did not exhibit any of these symptoms. The disease was prevented by ascorbic acid. One milligram of ascorbic acid per day maintained health in guinea pigs receiving 5 per cent of glucoascorbic acid, and 10 milligrams of ascorbic acid per day protected animals receiving 7 per cent glucoascorbic acid. The disease is therefore regarded as an ascorbic acid deficiency and glucoascorbic acid may be added to the list of newly recognized anti-vitamins. *Federation Proc. 3,* 97 (1944).

NUTRITION IN TROPICS—A recent report indicates that dietary needs are, in general, qualitatively similar in hot and in temperate climates. Quantitatively, however, the requirements for certain constituents may be altered in hot climates, by increased losses in sweat, by anorexia and by the specific effects of heat. The prevention of heat stroke, heat dehydration and heat cramps, and the maintenance of efficient physical performance, offer a guide to the assessment of a number of food requirements. Water shortage, resulting in the exhaustion of dehydration, is very easily induced. To prevent the deficiency syndrome, men should always be maintained in water balance. Actual requirements depend on environmental conditions, on the degree of activity, and on individual idiosyncrasies in the rate of sweating. Deficiency of sodium chloride soon leads to poor performance, heat exhaustion and eventually heat cramps. Exact requirements depend on surrounding conditions, on the degree of physical activity, and on the composition of the sweat. Sedentary men rarely need more than 10 grams of salt a day, working men need 15 to 20 grams. Salt should be given in the drinking water, in a concentration not greater than 0.2 per cent. Recent research has not confirmed earlier reports of considerable losses of water soluble vitamins in the sweat, especially of vitamin B_1 and ascorbic acid. It has been found that fit men can carry out work satisfactorily in hot climates for a period of a week on a low calorie supply, losing body fat to the extent of 5 to 10 per cent. of the bodyweight, without ill effect. This is of importance in regard to the issue of rations for short periods. —*Nutr. Abstr. & Rev. 14,* 118 (1944).